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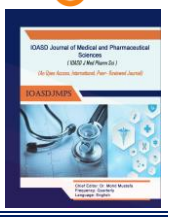

The Immunohematology of Hyperglycemia: Laboratory Evidence and Hematological Changes

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ABSTRACT

Hyperglycemia, whether acute or chronic, has extensive harmful consequences on both the haematologic and immunological systems. In addition to its well-known effects on metabolism, high blood sugar levels for a long time can seriously mess up cellular homeostasis and the integrity of blood vessels. High levels of glucose change the shape, flexibility, and longevity of red blood cells (RBCs), making it harder for them to carry oxygen and causing problems with the microcirculation. At the same time, hyperglycemia changes the way white blood cells move, stick to things, move around, and eat things, which weakens both innate and adaptive immune responses. Additionally, hyperglycemia promotes platelet activation and aggregation, fostering a pro-thrombotic and pro-inflammatory environment that increases the risk of vascular problems. Long-term exposure to high glucose causes non-enzymatic glycation of membrane proteins and haemoglobin. This creates advanced glycation end products (AGEs) that cause oxidative stress, problems with the endothelium, and problems with the immune system. These molecular occurrences jointly foster low-grade systemic inflammation, compromised haemostasis, and modified cellular signalling pathways.

Keywords: Immunohematology, Hyperglycemia Laboratory, Hematological Changes.

Review Article

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INTRODUCTION

Diabetes mellitus and kindred hyperglycaemic conditions are well-known for their significant metabolic dysregulation, marked by a sustained increase in blood glucose levels resulting from deficiencies in insulin secretion, insulin action, or both. Nonetheless, although the metabolic facets of diabetes—including hyperglycemia, dyslipidaemia, and disrupted carbohydrate metabolism—are comprehensively characterised, the haematologic and immunologic ramifications of these abnormalities are frequently overlooked. Chronic hyperglycemia affects more than just energy metabolism; it has a big effect on almost all parts of the immunological and haematopoietic systems. Continued exposure of blood cells to high glucose levels causes a series of biochemical, structural, and functional changes that are important in both the lab and the clinic [1].

Hyperglycemia alters erythrocyte membrane characteristics by non-enzymatic glycation, diminishing red cell deformability and longevity, potentially leading to tissue hypoxia and anaemia of chronic illness. Oxidative stress and inflammation also damage the function of leukocytes, which makes phagocytosis less effective, chemotaxis less effective, and the inflammatory environment more likely to cause repeated infections and slow wound healing. Platelet hyperactivity and increased coagulation exacerbate the situation, fostering a prothrombotic condition that is fundamental to numerous vascular problems linked to diabetes [2]. These changes in the blood and immune system have big effects on how diseases progress and how likely they are to get well. They play a big role in the development of both microvascular (retinopathy, nephropathy, neuropathy) and macrovascular (atherosclerosis, coronary artery disease, stroke) issues that are common in people with diabetes for a long time. They also change how the body defends itself, making people more likely to get bacterial and fungal infections and slowing down the healing of damaged tissues [3].

Consequently, comprehending the immunohematologic dimensions of hyperglycemia is crucial for the thorough management of diabetic individuals as well as for the prompt diagnosis and

assessment of disease severity. Examining blood cell indices, inflammatory markers, and coagulation factors in a lab can give us important information on how long-term high blood sugar affects the body. These assessments allow healthcare professionals and laboratory personnel to detect subclinical problems, categorise patient risk, and refine treatment approaches. For researchers, these results provide insight into the molecular and cellular pathways linking metabolic and haematologic dysfunctions, highlighting the integrative nature of diabetes as a systemic condition. Laboratory Evidence of Haematological Alterations in Hyperglycemia [4].

An increasing accumulation of laboratory and clinical evidence highlights that hyperglycemia—regardless of its manifestation in type 1 or type 2 diabetes mellitus, gestational diabetes, or temporary stress-induced conditions—produces significant and quantifiable impacts on haematological parameters. These alterations signify the systemic impact of glucose dysregulation on erythropoiesis, leukopoiesis, platelet formation, and the functional integrity of circulating blood cells.
In type 2 diabetes mellitus (T2DM), numerous extensive studies have delineated certain haematologic abnormalities linked to chronic hyperglycemia. A thorough cross-sectional investigation with 1,000 diabetes patients in Saudi Arabia revealed that inadequately managed glycemia markedly affects red cell indices. The study indicated that the mean red blood cell (RBC) count, mean corpuscular volume (MCV), mean corpuscular haemoglobin (MCH), and mean corpuscular haemoglobin concentration (MCHC) were significantly increased in hyperglycaemic people relative to non-diabetic controls. The red cell distribution width (RDW), an indicator of anisocytosis, exhibited an inverse correlation with glycaemic management, indicating that hyperglycemia may promote the generation of more uniform, but frequently structurally impaired, erythrocytes. Furthermore, individuals with microvascular and macrovascular problems had a reduced RBC lifespan, correlating with heightened membrane glycation, oxidative stress, and accelerated erythrocyte destruction.

A comparative examination of managed and uncontrolled diabetic individuals further validated these findings. In subjects exhibiting inadequate glycaemic management (characterised by glycated haemoglobin [HbA1c] levels over 7%), haematologic profiles demonstrated a significant increase in total leukocyte count, specifically in monocytes, basophils, and neutrophils. Derived inflammatory indices, including the neutrophil-to-lymphocyte ratio (NLR), platelet-to-lymphocyte ratio (PLR), mean platelet volume (MPV), platelet distribution width (PDW), and plateletcrit (PCT), were significantly elevated in the uncontrolled group, highlighting the pro-inflammatory and pro-thrombotic milieu induced by persistent hyperglycemia. On the other hand, the same group showed lower levels of RBC count, haemoglobin concentration, and MCV. These results show how glycaemic toxicity hurts erythropoiesis and red cell stability [5].
These findings align with extensive epidemiological data. A new meta-analysis including over 14,000 individuals aggregated data from various populations and determined that in Type 2 Diabetes Mellitus (T2DM), total white blood cell counts—including neutrophils, basophils, lymphocytes, and monocytes—are consistently higher. This leukocytosis signifies low-grade systemic inflammation, a well-established characteristic of insulin resistance and vascular damage. Conversely, erythrocytic indices, including haemoglobin concentration and haematocrit, were markedly diminished relative to non-diabetic controls, indicating that hyperglycemia induces a functional anaemia influenced by oxidative stress and renal impairment (due to decreased erythropoietin production) [6].

The pattern in type 1 diabetic mellitus (T1DM) seems to be a little less clear, although still follows the same general tendency. Research conducted on Ethiopian adults with T1DM indicated that about one-third of the patients were anaemic, but more than three-quarters had leukocytosis. Male participants and individuals with an extended period of disease exhibited the most significant haematological abnormalities, suggesting a cumulative impact of chronic hyperglycemia and immunological dysregulation over time [7].

In gestational diabetes mellitus (GDM), haematologic problems may manifest more aggressively yet are of comparable significance. Persistent hyperglycemia during pregnancy has been demonstrated to alter erythrocyte morphology, creating a spectrum of abnormalities including microcytosis, hypochromia, anisocytosis, poikilocytosis, target cells, and macrocytes. These morphological changes are similar to the long-term metabolic and oxidative stress caused by high blood sugar levels. They may also make blood thicker, make the placenta work less well, and make it harder for the foetus to get oxygen [9].

These laboratory results demonstrate that hyperglycemia disturbs haematologic homeostasis via various interconnected mechanisms, including the glycation of structural proteins, oxidative membrane damage, modified cytokine signalling, and the activation of inflammatory processes. The outcome is a haematologic profile characterised by low-grade inflammation, erythrocyte fragility, platelet hyperactivity, and compromised oxygen transport, all of which synergistically exacerbate the vascular and immunologic consequences of diabetes mellitus [10].

Mechanisms Responsible for Haematological and Immune Changes

The mechanisms driving these haematologic and immunologic alterations are complex, involving

biochemical, molecular, and physiological processes. One of the main ways is non-enzymatic glycation. Too much glucose causes haemoglobin to glycate, which makes HbA_1C, and it changes the proteins in the membranes of red blood cells. These changes make RBCs less flexible, make membranes stiffer, and make cells less likely to survive, which makes it harder for oxygen to get to them [11].

Oxidative stress is another important process. High blood sugar levels cause the body to make too much reactive oxygen species (ROS), which can damage lipids, proteins, and DNA. Red blood cells are more likely to have their membranes oxidised, which causes haemolysis and shortens their lives. White blood cells are not spared; their chemotactic and phagocytic activities are frequently compromised [12].

Hyperglycemia is also marked by inflammation and immunological activity. High blood sugar levels cause pro-inflammatory cytokines to be released, endothelial cells to be activated, and leukocyte adhesion to be increased. These processes result in systemic inflammation, frequently shown by increased total leukocyte counts, enhanced neutrophil levels, and higher neutrophil-to-lymphocyte (NLR) and platelet-to-lymphocyte (PLR) ratios. Other pathways involve changes in osmotic balance, where hyperosmolar conditions lead to cellular dehydration or swelling due to changes in water content, which affects MCV and MCH. Chronic vascular damage and microangiopathy further impede blood flow to the bone marrow, hinder haematopoiesis, and facilitate haemolysis. Platelet activation and coagulation abnormalities are equally important. Glycation of platelet membranes, oxidative stress, and dysregulated signalling all make platelets more reactive and more likely to form clots. Long-term hyperglycemia, especially when combined with kidney failure or a lack of nutrients, can slow down the generation of red blood cells and upset the usual balance of blood cell synthesis in the bone marrow [13]

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Haematologic and immunologic parameters impacted.

There are a lot of different changes in the blood and immune system that can happen when blood sugar levels are high. In uncontrolled diabetes, particularly type 1, red blood cell indices frequently decrease; however, certain investigations have seen modest erythrocytosis or hemoconcentration in early type 2 diabetes attributed to dehydration. Lower levels of haemoglobin and haematocrit make it harder for the body to carry oxygen, which might make you tired and make you more likely to have ischaemic attacks. It can also mean that you might have anaemia of chronic disease or kidney disease [14].

In certain populations with type 2 diabetes, indices including MCV, MCH, and MCHC may experience slight increases, but RDW is typically increased, signifying anisocytosis and compromised erythropoiesis. In gestational diabetes, prominent red cell morphological abnormalities may serve as valuable indications of disease severity. White blood cells often have higher total counts and higher counts of other types of cells, like neutrophils and lymphocytes. The NLR is a simple but strong sign of inflammation. It is generally greater in people with uncontrolled diabetes, which means they are more likely to have complications and have a higher risk of systemic inflammation. Platelet counts and indices—like MPV, PDW, platelet-large cell ratio (P-LCR), and PCT—are also higher, which means that platelets are more active and more likely to form clots. Immune cell activity deteriorates, characterised by poor neutrophil chemotaxis and phagocytosis, diminished lymphocyte proliferation, and attenuated responses to pathogens. This explains the heightened susceptibility to infections and delayed wound healing observed in diabetic patients. Coagulation profiles and hemorheology indicate heightened blood viscosity, diminished red cell deformability, and an overall transition towards a hypercoagulable state, all of which augment the risk of thrombotic and cardiovascular incidents [15].

Diagnostic and Prognostic Consequences

Haematological indices and derived ratios, including NLR, PLR, and RDW, are cost-effective and readily available laboratory tests that may function as early indications of inadequate glycaemic control or the onset of problems. Importantly, many of these haematologic anomalies seem to go away when blood sugar levels are well controlled. Patients who have better glycaemic management have seen their high white cell and platelet indices go down. This shows how useful they could be for tracking disease [16]. Anaemia in diabetes frequently arises from a confluence of renal dysfunction, dietary inadequacy, and persistent inflammation. Understanding the haematologic contribution might lead to quick assessment of kidney function and iron levels. Gestational diabetes has a haematologic effect on pregnant women that can affect both their health and the health of their unborn child. This means that prenatal screening and follow-up are very important [17].

Furthermore, even while there is constant proof of changes in the blood in people with high blood sugar, there are still some problems. Most research are still cross-sectional, which makes it hard to draw conclusions about cause and effect [18]. The study populations exhibit significant variability in diabetes type, disease duration, comorbidities, and demographic variables, hence complicating data interpretation. Different institutions utilise different laboratory methods and reference ranges, and things like dehydration, medication use, or other causes of anaemia are not always taken into account. Functional tests of immune cells are intricate and not consistently standardised, resulting in immune failure typically being assumed rather than directly evidenced [19].

CONCLUSION

Hyperglycemia has quantifiable impacts on both the immunological and haematologic systems, resulting in a unique laboratory signature indicative of metabolic dysregulation. These modifications, which include changes in red blood cell indices and leukocyte profiles, platelet activation, and coagulation, have important diagnostic and prognostic consequences. Routine haematological measures, due to their cost-effectiveness and widespread availability, can yield significant insights into disease severity, inflammation, and the risk of consequences. Ongoing longitudinal and mechanistic studies across varied populations are essential to clarify the reversibility of these anomalies and to enhance their function in clinical therapy and prognosis.

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